ORIGINAL ARTICLE
ARTIGO ORIGINAL

Cost effectiveness analysis of plasma genotyping *versus* tumor genotyping in detection of advanced non-small-cell lung cancer with epidermal growth factor receptor and T790M mutation under the Brazilian private healthcare system perspective

Custo-efetividade do uso da biópsia líquida versus *biópsia tecidual para detecção de câncer de pulmão de não pequenas células avançado com receptor do fator de crescimento epidérmico e mutação T790M sob a perspectiva do sistema suplementar de saúde do Brasil*

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Keywords:
non-small cell lung cancer, cost benefit analysis, genotyping techniques, epidermal growth factor receptor

ABSTRACT

Objective: Comparing the costs and effectiveness of plasma genotyping versus tumor genotyping for detecting the T790M mutation in advanced non-small cell lung cancer (NSCLC) with a mutation in the epidermal growth factor receptor (EGFR) and that progressed after use of an EGFR tyrosine kinase inhibitor (EGFR-TKI), from the perspective of the private healthcare system in Brazil. **Methods:** Patients with a post-EGFR-TKI T790M mutation are eligible for a second-line treatment with a third--generation EGFR-TKI (osimertinib). In order to estimate the costs associated with the diagnosis method for the T790M mutation, a decision tree model has been used. Resource use was estimated by a team of experts, and the direct costs were estimated based on official databases. **Results:** Plasma genotyping provided a R$391 reduction per patient, due to the reduced cost with complications; it prevented 40.96% of the patients from undergoing an invasive procedure and 31.91% of the patients from having any kind of complication. **Conclusion:** Data found support a new paradigm for treating the resistance to EGFR-TKIs, with plasma genotyping as the first diagnostic choice, what can help to define the treatment and to reduce the costs of Brazilian private healthcare system.

Palavras-chave:
câncer de pulmão de não pequenas células, análise custo-benefício, técnicas de genotipagem, receptor do fator de crescimento epidérmico

RESUMO

Objetivo: Comparar os custos e efetividade da biópsia líquida *versus* biópsia tecidual para detecção da mutação T790M no câncer de pulmão de não pequenas células (CPNPC) avançado com mutação no receptor do fator de crescimento epidérmico (*EGFR*) e que progrediram após o uso de um inibidor do sítio da tirosina cinase associada ao EGFR (EGFR-TKI), sob a perspectiva do sistema suplementar de saúde do Brasil. **Métodos:** Pacientes com mutação EGFR-T790M pós-EGFR-TKI são elegíveis ao tratamento de segunda linha com um EGFR-TKI de terceira geração (osimertinibe). Para a estimativa dos custos relacionados ao método de diagnóstico de mutação T790M, foi elaborado

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um modelo de árvore de decisão. A utilização de recursos foi estimada por painel de especialistas e os custos diretos foram estimados utilizando-se bases de dados oficiais. **Resultados:** A biópsia líquida proporcionou redução de R$ 391 por paciente, devido a uma redução no custo com complicações; evitou que 40,96% dos pacientes passassem por um procedimento invasivo e que 31,95% dos pacientes tivessem algum tipo de complicação. **Conclusão:** Os dados observados embasam um novo paradigma para o manejo da resistência aos EGFR-TKIs, com genotipagem pelo plasma como primeira opção diagnóstica, o que pode auxiliar na melhor definição do tratamento e reduzir custos ao sistema de saúde suplementar brasileiro.

Introduction

Nowadays, considering the locally advanced or metastatic lung cancer scenario, the decisions regarding treatment choice are not only based on histological characteristics, but also include information on genetic changes that can identify different, molecularly defined subtypes. Lung tumors carrying mutations in the gene of the epidermal growth factor receptor (EGFR) are examples of biomarkers predicting this disease. These mutations are identified on exons 18 through 21 in the tyrosine kinase (TK) domain of the EGFR and consist of both occasional mutations and small deletions or insertions (Fenizia *et al.*, 2015).

EGFR mutations can be defined as "activators", since they determine the activation of the TK domain regardless of the ligand, which leads to an increase in cell proliferation and survival; they can be considered associated with drug sensitivity, given the fact that they cause an increase in EGFR sensitivity by tyrosine kinase inhibitors (TKIs) – such as gefitinib, erlotinib, and afatinib – which results in lower required drug concentration to inhibit the receptor phosphorylation. Not all EGFR gene mutations are associated with drug sensitivity. There are also mutations associated with drug resistance. T790M mutation is an example of a mutation that creates resistance to first- and second-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs); however, this mutation is related to third-generation EGFR-TKI sensitivity. In this setting, as the mutational status of EGFR is relevant for choosing the most adequate therapy, assessing EGFR mutations has become a mandatory clinical practice. Currently, different techniques are available for assessing genetic changes in the EGFR gene. Generally, the most common screening methods for EGFR mutations are polymerase chain reaction (PCR), Sanger sequencing, limited by their low sensitivity, new generation sequencing (NGS), pyro sequencing, high-resolution melt analysis (HRMA), and single-strand conformation polymorphism (SSCP) analysis. However, one of the biggest challenges for these molecular tests is the source of the biological material (Fenizia *et al.*, 2015).

In the current scenario, tumor genotyping is considered the gold standard for genotyping. Although the necessity of tissue for the diagnosis of the disease and further histological analysis, frequently there is no enough tissue for genotyping. It should also be highlighted that, once the tissue is worn out, options include repeating the biopsy or, more frequently, offering the patient an empirical treatment with standard chemotherapy, when the patient could benefit from a target therapy (Buder *et al.*, 2016; Crowley *et al.*, 2013; Villaflor *et al.*, 2016), which is deemed to be suboptimal these days. Besides, depending on the sample, the tumor genotyping procedure creates an extremely variable quantity of tumor cells. As a consequence, the amount and quality of the extracted DNA can be affected by the process of tissue acquisition, sample preservation, and tumor heterogeneity, which can lead to false-positive or false-negative results (Fenizia *et al.*, 2015). Other limitations include the discomfort sustained by the patient and potential surgical and clinical complications arising from this procedure (Buder *et al.*, 2016; Crowley *et al.*, 2013; Diaz & Bardelli, 2014). With respect to economic aspects, using tumor genotyping leads to multiple invasive procedures throughout the course of the disease, increasing the total cost of the patient's care (Villaflor *et al.*, 2016; Ilie & Hofman, 2016).

Considering the limitations for tumor genotyping, identifying molecular changes by using alternative DNA sources, such as blood samples, serum, and plasma, called plasma genotyping, can become an interesting strategy in cases where a tissue specimen or good quality biopsy is not available (Fenizia *et al.*, 2015; Buder *et al.*, 2016; Villaflor *et al.*, 2016). The clinical applications of plasma genotyping include defining treatment, monitoring tumor response to therapy, and determining clinical scenarios as stable disease or mixed responses. In addition, changes in circulating tumor DNA (ctDNA) can predict early responses to treatment in the course of the therapy, which can allow a real-time modification follow up of the treatment regimen in research setting (Diaz & Bardelli, 2014).

Plasma genotyping can be used for diagnosing the T790M mutation in patients with advanced NSCLC, following treatment with EFGR-TKI, and its accuracy has been analyzed in clinical trials (Oxnard *et al.*, 2016; Takahama *et al.*, 2016; Thress *et al.*, 2015; Zheng *et al.*, 2016; Sundaresan *et al.*,

2016; Wang *et al.*, 2017). According to the results, evidence of viability and clinical utility of plasma genotyping for treating patients with NSCLC in the post-EGFR-TKI progression period was found. Generally, the sensitivity for detecting the T790M mutation in plasma was up to 70%, depending on the study and the analysis method employed. The information found from selected evidence has revealed that plasma genotyping for detecting the mutational status of EGFR has important clinical applications, such as supplementing or replacing more expensive and invasive methods to assess response in EGFR--TKI-treated patients, permitting an early detection of T790M mutation and the potential change of subsequent therapy approach, with the choice of the best treatment regimen for patients (Marchetti *et al.*, 2015).

Furthermore, the easiness and reduced risk provided by the plasma analysis when compared to an invasive genotyping procedure are worth mentioning. Since blood--based genotyping procedures are minimally invasive, the sample can be collected with no considerable morbidity for the patient (Buder *et al.*, 2016).

Private healthcare system in Brazil

Brazil is the largest country in Latin America, with almost 210 million inhabitants and per capita GDP of US$ 15,200 as of 2017 (The World Fact Book). Ever since the 1988 Constitution, all Brazilians have the right to free-of-charge healthcare through a national healthcare system (SUS), which is unique in the continent, funded by taxes and insurance payments (Victora *et al.*, 2011). In addition, about 20%-25% of the population has a private health insurance plan (Ferreira CG *et al.*, 2016). Currently, the country spends US$ 1,318 per capita with healthcare, a little bit more than 8% of its GDP, which is near the average of Latin America. Nevertheless, these numbers include both public and private expenditure, and there is a huge inequity between these two systems. This 25% share of the population, who have access to private healthcare, represents over 54% of the total amount, whereas less than half of the total healthcare budget is directed to the remaining 75% of the population, who rely on SUS only (Atun *et al.*, 2015).

The Brazilian private healthcare system is governed by law 9656, enacted in 1998 (Brasil, 1998). Ever since, all patients who have a private health insurance have access, if necessary, to all procedures included on a list published by the National Health Agency (ANS), called "ANS ROL". Such document goes through a technical review process every two years by an experts committee. This board, called *Comitê Permanente de Regulação da Atenção à Saúde* [Permanent Healthcare Regulation Committee] – COSAÚDE, includes several stakeholders, and it takes into account criteria such as efficacy, cost, and available infrastructure for technology using all around the country (Agência Nacional de Saúde Suplementar). In Brazil, there is not a clear definition of cost effectiveness limit, even though discussions have taken place for an agreement. Submissions for this group's review can be made by medical entities, professional boards, healthcare institutions representatives, consumer protection authorities, or patient advocacy groups. After a technical review, the results are submitted for public consultation. Private healthcare organizations are free to extend their coverage beyond the procedures contained in this list, however, the premium amounts are adjusted based on that list, considering only the new procedures that will be on it.

The current refund system in Brazil, for private care, is based on a fee-for-service strategy and usually does not pay for the identification and treatment of patients who would be responders only, what unable the exclusion of those who will not benefit or might be harmed. Many high-cost diagnostic tests are not covered by health insurance companies. And the traditional fee-for-service refund, as usual, offers incentives for service applications based on volume, rather than on aggregate value (Pritchard *et al.*, 2017).

In this context, this analysis aims to provide clinical and economic evidence to support the use of plasma genotyping for detecting T790M mutation in locally advanced or metastatic NSCLC with EGFR mutation that progressed following use of an EGFR-TKI, in the private healthcare system in Brazil.

Methods

Model structure: the type of analysis chosen was the cost effectiveness analysis as the purpose of this model is comparing the direct medical costs involved in detecting a T790M mutation in locally advanced or metastatic NSCLC, with EGFR mutation, which progressed following use of an EGFR-TKI.

To estimate the costs, a (short-term) decision tree model was developed, with an option to follow either the tumor genotyping or the plasma genotyping arm (Figure 1).

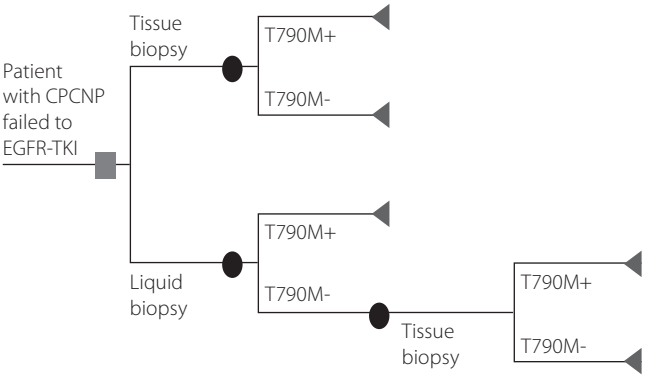

Figure 1. Model structure – Decision Tree.

Specificity and sensitivity data

Specificity and sensitivity of the genotyping testing

The specificity and sensitivity of tumor genotyping was considered to be 100%. For plasma genotyping, sensitivity and specificity were considered to be 51.25% and 77.07%, respectively (Jenkins *et al.*, 2017).

Table 1 shows the percentages of positive and negative tests for each of the genotyping types (Jenkins *et al.*, 2017).

Tumor genotyping-related complications

The events of complications relating to tumor genotyping considered were: breathing difficulty (41%), severe chest pain (23%), and pneumothorax (14%) (Karve *et al.*, 2016).

Cost data – Cost for the genotyping tests

To estimate the cost for tumor genotyping, any potential procedures that can be used for performing the exams were considered, as well as the corresponding use rates, based on experts' opinion: fine-needle percutaneous biopsy, bronchoscopy, thoracocentesis, nodule removal, and EGFR testing. In addition, the cost for any complications related to tumor genotyping was included. Table 2 shows the cost for tumor genotyping. The costs for each procedure were taken from an official database in Brazil (Revista Simpro Hospitalar, 2016; CBHPM, 2017).

Table 1. Percentage of patients diagnosed per type of testing

Exam	T790M+	T790M-
Tumor genotype (Cobas®, Central Laboratory)	359/564 (63.65%)	205/564 (36.35%)
Plasma genotype (BEAMing)	231/564 (40.96%)	333/564 (59.04%)

T790M+: Patient with a T790M mutation in the epidermal growth factor receptor. T790M-: Patient without a T790M mutation in the epidermal growth factor receptor.

Table 2. Tumor genotyping cost

Cost items	% of use	Unit Cost	Total Cost
Fine-needle percutaneous biopsy	42.0%	R$ 1,056.64	R$ 443.79
Bronchoscopy	53.0%	R$ 1,641.89	R$ 870.20
Thoracentesis	2.5%	R$ 3,224.47	R$ 80.61
Nodule Removal	2.5%	R$ 24,824.69	R$ 620.62
EGFR test	100%	R$ 1,800.00	R$ 1,800.00
Complications	-	R$ 3,513.96	R$ 3,513.96
• Difficulty breathing	41.0%	R$ 2,872.03	R$ 1,177.53
• Severe chest pain	23.0%	R$ 4,724.64	R$ 1,086.67
• Pneumothorax	14.0%	R$ 8,926.83	R$ 1,249.76
Total cost			**R$ 7,329.17**

For plasma genotyping a cost of R$2,000 per exam was considered.

Results

Cost effectiveness analysis

The cost and efficacy results of the tests were assessed according to the decision tree described above.

Table 3 shows the percentage of T790M patients identified and the percentage of complications per type of genotyping test. Table 4 shows the costs associated with each genotyping test.

The use of plasma genotyping provided a reduction of R$ 391 per patient due to a cost reduction with complications associated with the tissue biopsy procedure. In addition, it prevented 40.96% of the patients from undergoing an invasive procedure to detect the mutation and 25.45% of the patients from experiencing any kind of complication.

Sensitivity analysis

A univariate sensitivity analysis was conducted with the purpose of assessing the uncertainties related to the model through the variation of certain parameters. The parameters were: (i) cost and occurrence of the complications, difficulty breathing, severe chest pain, and pneumothorax; (ii) costs involved with tissue biopsy, fine-needle percutaneous biopsy, bronchoscopy, thoracocentesis, nodule removal, and EGFR test; (iii) proportion of T790M patients + in tissue biopsy; (iv) cost, sensitivity and specificity of the plasma genotyping. With exception of tissue biopsy sensitivity and specificity, the further parameters were varied 10% up or down. The sensitivity varied between 46% and 57%, and the specificity between 71% and 73%, according to the confidence intervals established in the study (Jenkins *et al.*, 2017).

Despite the individual variation of the parameters in its corresponding lower and upper limits, the use of plasma genotyping showed a lower cost when compared to the tumor genotyping. Among the values obtained by iterations, a reduction from R$ 145.99 to R$ 659.16 in favor of tumor genotyping was observed.

Figure 2 shows the parameters with higher impact on the cost results.

Discussion

Our results suggest that, in the short-term, the use of plasma genotyping reduces in R$ 391 the cost per patient for the healthcare insurance provider in the setting of Brazilian private healthcare system, due to a relevant reduction in the cost of complications associated with tumor genotyping, in addition to preventing 40.96% of these subjects from undergoing an invasive procedure and 25.45% from experiencing a clinically significant complication derived from these procedures. It indicates that the procedure can be considered for those patients with locally advanced or metastatic non-small cell

Table 3. Efficacy results

Clinical endpoint	Plasma genotyping		Tumor genotyping	Incremental
	Plasma genotyping*	Plasma genotyping followed by tumor genotyping†		
% of patients T790M+	40.96%	71.99%	63.65%	8.33%
True-positive	32.62%	63.65%	63.65%	0.00%
False-positive	8.33%	8.33%	0.00%	8.33%
True-negative	28.01%	28.01%	36.35%	-8.33%
False-negative	31.03%	0.00%	0.00%	0.00%
Complications‡	0%	52.55%	78.00%	-25.45%
Difficulty breathing	0%	27.62%	41.00%	-13.38%
Severe chest pain	0%	15.50%	23.00%	-7.50%
Pneumothorax	0%	9.43%	14.00%	-4.57%

* Result of the plasma genotyping test.
† Result of the tumor genotyping test after plasma genotyping test in patients with negative result for mutation T790M in the plasma genotyping test.
‡ Complication related to the patient with negative plasma genotyping test who required tumor genotyping to confirm the result.

Table 4. Cost results

Costs	Plasma genotyping		Tumor genotyping	Incremental
	Plasma genotyping*	Plasma genotyping followed by tumor genotyping†		
Exams/Procedures	R$ 2,000.00	R$ 4,570.54	R$ 3,815.22	R$ 755.32
Complication‡	R$ 0.00	R$ 2,367.56	R$ 3,513.96	-R$ 1,146.40
• Difficulty breathing	R$ 0.00	R$ 793.37	R$ 1,177.53	-R$ 384.16
• Severe chest pain	R$ 0.00	R$ 732.15	R$ 1,086.67	-R$ 354.52
• Pneumothorax	R$ 0.00	R$ 842.03	R$ 1,249.76	-R$ 407.72
Total	**R$ 2,000.00**	**R$ 6,938.10**	**R$ 7,329.17**	**-R$ 391.08**

* Result of the plasma genotyping test.
† Result of the tumor genotyping test after plasma genotyping test in patients with negative result for mutation T790M in the plasma genotyping test.
‡ Complication related to the patient with negative plasma genotyping test who required tumor genotyping to confirm the result.

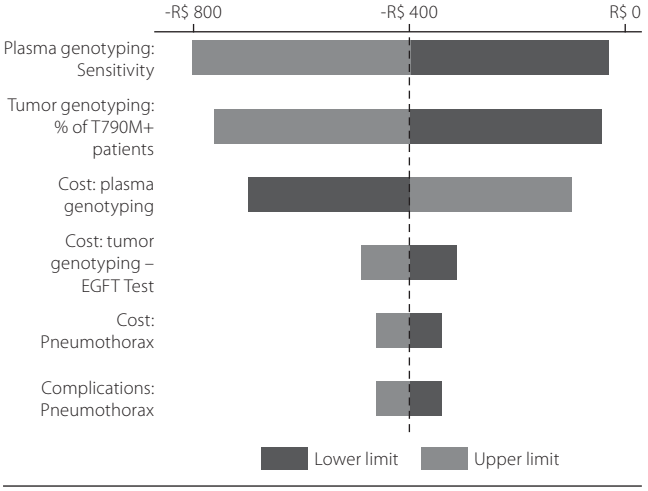

Figure 2. Tornado diagram

lung cancer and who eventually experience clinical progression after first line therapy with EGFR-TKIs (gefitinib, erlotinib or afatinib) to define the subsequent treatment. In this setting, in the presence of T790M mutation, the use of a third line EGFR inhibitor, osimertinib, showed to be superior to platinum-based chemotherapy and pemetrexed, according the Phase III, prospective study (Mok *et al.*, 2017). The information regarding the mutation is then essential for the result of patients' treatment. Considering this analysis, obtaining the information via plasma genotyping is cost-effective compared to the invasive procedure.

The conducted sensitivity analysis indicates that there is a cost reduction caused by the use of plasma genotyping with statistical significance. Namely, within the predetermined pa-

rameters limits, the use of plasma genotyping showed cost reductions in all the scenarios analyzed.

Detection of biological markers in the blood stream is not a new concept. For example, for many years the carcinoembryonic antigen (CEA), the prostate-specific antigen (PSA) or the Ca-125, among others, were used to assess the treatment response (Friedrich, 2017), defining the conduct subsequently taken, whether the clinical follow-up, maintenance of the treatment initially applied or even the search for an alternative treatment given the lack of response, which was observed with the marker increase (Murray *et al.*, 2015; Stremitzer *et al.*, 2015; Alexandre *et al.*, 2012). The plasma genotyping has the potential to bring a higher number of information, not only about the decision of whether to treat or not treat, but also about how to treat or how to optimize the treatment response. Defining exactly which subgroup of patients obtains benefit from a certain drug is a valuable information for prescribing doctors, patients and payers. The treatment of sensitive patients, as the non-treatment of the resistant patients, will increase the product efficacy, thus increasing the probability of not overcoming the cost effectiveness threshold of this treatment, whatever it may be (Salgado *et al.*, 2017). In a recent study, for example, the circulating DNA analyses were able to identify mutations in 85% of the patients, with high correlation with tumor genotyping of the corresponding tumors (Zill *et al.*, 2016).

The comparator, according to our model and considering the inferior achieved results with empirical treatment (Mok *et al.*, 2017), should be the tumor genotyping. And the plasma genotyping, compared to the tumor genotyping, has the initial advantage to allow obtaining relevant information for subsequent treatment for those patients for whom obtaining this material through invasive methods is not feasible. The plasma genotyping can be conducted through a simple and minimally invasive procedure, a vein puncture, since while the tumor may be difficult to access, veins are easily accessible. Additionally to the ease of obtaining the tumor sample, samples obtained through peripheral puncture may show how the tumor's molecular profile develops throughout the time, in response to many factor that may cause interference there, including the administered treatments (Friedrich, 2017). This may serve as *in vivo* monitoring of the therapeutic treatment administered.

Payers shall know how effective a treatment (or intervention) is compared to the available options, in order to have a complete vision of the scenario where decisions relative to reimbursement are performed. The lack of convincing data focused on relevant clinical endpoints, in addition to infrequent use of surrogate endpoints, are frequent obstacles in the acceptance of new technologies, in the usual clinical practice (Frueh, 2013). In the Brazilian private healthcare system, the situation is not different (Ferreira *et al.*, 2016). San Miguel & Hulstaert showed, in a recent article, that the test precision and its sensitivity and specificity are frequently more important for the final cost effectiveness ratio than the test price itself. The evaluation scope must be clear and relevant over the comparator; besides, the current local practice and the use of support treatments need to be considered on the studied circumstances (San Miguel & Hulstaert, 2015). Thus, our study brings robust data supporting that the use of plasma genotyping in the setting of the Brazilian Supplemental Health Care, in patients with non-small cell lung cancer who progressed following initial therapy with EGFR--TKIs may, is a cost-effective alternative, and that the patients should undergo plasma genotyping procedure to define the subsequent treatment.

Study limitations

This study has some limitations. Among those, the main one is that variations among the plasma genotyping, both in the source of biological material (CTC, ctDNA, and cfDNA) and the genotyping methods used (ddPCR, ARMS, BEAMing, NGS, Cobas® EGFR mutation test) may potentially lead to some variation in the results achieved.

Conclusion

In conclusion, the presented data support a new paradigm to be used in the treatment of patients with NSCLC and resistance to EGFR-TKIs with plasma genotyping as a diagnostic choice. The plasma genotyping can help the definition of the subsequent treatment prior to the conduction of tumor genotyping. In addition to the advantage to the patient, the plasma genotyping may generate economy of resources to the funding source under the Brazilian private healthcare system perspective.

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